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Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045

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TO: Commissioner for Patents
Attn: Examiner Patrick T. Lewis
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Alexandria, VA 22313-1450

FROM: Karen S. Canady
OUR REF.: G&C 30794.30-US-WO
TELEPHONE: (310) 642-4148

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Applicant:	Norbert O. Reich et al.
Serial No.:	09/485,071
Filed:	February 3, 2000
Group Art Unit:	1623
Title:	MODULATORS OF DNA CYTOSINE-5 METHYLTRANSFERASE AND METHODS FOR USE THEREOF
Our Ref. No.:	G&C 30794.30-US-WO

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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CERTIFICATE OF MAILING OR TRANSMISSION UNDER 37 CFR 1.8

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Name: Karen S. Canady

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

We are transmitting herewith the attached:

☒ Transmittal sheet, in duplicate, containing a Certificate of Mailing or Transmission under 37 CFR 1.8.
☒ Brief of Appellant(s).
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Los Angeles, CA 90045
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AUG 10 2005

Due Date: August 10, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Inventor: Norbert O. Reich et al.	)	Examiner: Patrick T. Lewis
	)	
Serial #: 09/485,071	)	Group Art Unit: 1623
	)	
Filed: February 3, 2000	)	
	)	
Docket No.: G&C 30794.30-US-WO	)	Appeal No.: _____
	)	

Title: MODULATORS OF DNA CYTOSINE-5 METHYLTRANSFERASE AND METHODS FOR USE THEREOF

BRIEF OF APPELLANTS

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR §41.37, Appellants hereby submit the Appellants' Brief on Appeal from the final rejection in the above-identified application, as set forth in the Office Action dated March 10, 2005.

Please charge the amount of $250 to cover the required fee for filing this Appeal Brief as set forth under 37 CFR §41.37(a)(2) and 37 CFR §41.20(b)(2) to Deposit Account No. 50-0494 of Gates & Cooper LLP.

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I. REAL PARTY IN INTEREST

The real party in interest is The Regents of the University of California, the assignee of the present application.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for the above-referenced patent application.

III. STATUS OF CLAIMS

Claims 31, 36, 37, 39, and 43-48 are pending in the application. Claims 36-37, 39, 43-45, and 47-48 were rejected under 35 U.S.C. §103(a) as being unpatentable in view of the combination of Flynn et al. (Flynn), Biochemistry (1996), Vol. 35, pages 7308-7315 (Appellants note that, although the Office Action cites Flynn as a 1986 publication, the actual publication date was 1996) and Billing-Medal et al. (Billing), U.S. Patent No. 6,183,952, and these rejections are being appealed.

IV. STATUS OF AMENDMENTS

No amendments to the claims have been made subsequent to the final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Briefly, Appellants' invention, as recited in independent claims 31, 43, and 46, is directed to an invention that provides a synthetic oligonucleotide that inhibits DNA cytosine-C^5 methyl-transferase (DCMTase) by acting at a previously unknown allosteric site on the enzyme. The synthetic oligonucleotide of the invention is at least 26 nucleotides in length and comprises a 5mCpG dinucleotide, wherein the 5mC is a C-5 methylcytosine, and comprises the nucleotide sequence shown in SEQ ID NO: 10, wherein the synthetic oligonucleotide comprises a phosphorothioate nucleotide. In some embodiments, the synthetic oligonucleotide is presented as a pharmaceutical composition or as a

pharmaceutically acceptable salt. As shown in Figure 1B of Appellants' patent application, the synthetic oligonucleotide having the nucleotide sequence shown in SEQ ID NO: 10 has a surprising and unexpectedly superior efficacy, with an IC50 of 5 nM, which is far greater than that of, for example, the CRE aMET sequence (SEQ ID NO: 11) at an IC50 of >300 nM.

While it was previously known that antisense oligonucleotides that interfere with expression of DCMTase may inhibit tumorigenesis, and that the anticancer agent 5-aza-deoxycytidine functions by inhibiting the DCMTase, 5-Aza-deoxycytidine is unstable in solution and may be carcinogenic as well as mutagenic (see carryover paragraph at pages 4-5 of the specification). The state of the art at the time Appellants' application was filed was such that there remained a need for DCMTase inhibitors that do not require incorporation into DNA and that are mechanistically unlike 5-aza-deoxycytidine. Appellants' claimed invention fulfills this need and overcomes this problem by providing an inhibitor of DCMTase that does not require incorporation into DNA and operates via a different mechanism, as it binds to an allosteric site on the enzyme.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 36-37, 39, 43-45, and 47-48 are unpatentable under 35 U.S.C. § 103(a) as being rendered obvious by Flynn, Biochemistry (1996), Vol. 35, pages 7308-7315 and Billing, U.S. Patent No. 6,183,952.

VII. ARGUMENT

A. The Independent Claims Are Patentable Over The Prior Art

The Examiner's rejection of the claimed invention as unpatentable over the combination of Flynn and Billing relies on an erroneous assumption that any nucleotide that mimics DNA-regulatory elements known to have cytosine C-5 methylated regulation and capable of serving as a substrate for DCMTase would, by virtue of the forgoing properties, be an obvious choice to one of skill in the art to modify for use as a pharmaceutical composition. While Appellants do not dispute the art-recognized association between molecules that modulate DCMTase activity and anti-cancer therapeutic use (which is discussed at length in the Background section of the specification), Appellants disagree that one skilled in the art would consider it obvious to use any DCMTase

substrate that mimics DNA-regulatory elements as a therapeutic agent. This presumed association between any such substrate and anti-cancer therapeutic use relies on the erroneous assumption that all substrates having these properties would be expected to inhibit DCMTase. Appellants' own specification (see, e.g., Figure 1B) proves this assumption incorrect, as not all substrates tested were capable of inhibiting DCMTase activity.

The 1996 Flynn Biochemistry article (by the inventors) was designed to define suitable kinetic methods to investigate structure-function questions relating to the mammalian DCMTase, to apply such methods to quantify the enzyme's discrimination between related DNA sequences as well as between single-stranded and hemi-methylated DNA, and to identify the underlying binding and catalytic contributions to any observed discrimination (p. 7310, carryover paragraph of cols. 1-2). The study focused on two DNA sequences: one containing the cyclic AMP responsive element, CRE, and the other containing a GC-box, which is an Sp1 transcription factor recognition element. The article reports that both the CRE and GC-box sequences show burst kinetics, with the methylation of these substrates being significantly faster than steady-state turnover. The article also reported methylation rates and relative specificity of DCMTase, as well as comparisons of kinetic parameters between mammalian and bacterial DCMTases.

Nowhere in the text of the 1996 Flynn article is the suggestion made or implied that any of the substrates tested therein, including the GC-box sequence as well as the CRE sequence, is an inhibitor of DCMTase. Even the explanation provided by the Examiner in the Advisory Action dated June 2, 2005, fails to explain the basis for leaping from Flynn's description of substrates designed to mimic DNA transcriptional cis elements to the allegedly obvious use of these substrates in a therapeutic context. The Advisory Action does discuss the association between regulation of the enzyme and treatment of cancer, which Appellants concede. What remains utterly unaddressed is how one skilled in the art would have a reasonable expectation of success using these substrates to treat cancer ***without knowing of their inhibitory activity***, let alone the remarkably enhanced inhibitory activity of the phosphorothioate modified GC-box b^{MET} substrate.

For example, the leap from the premise to the conclusion is set forth in this basis for the rejection in the March 10, 2005 Office Action. At page 11 of the Office Action, the Examiner argues that "Flynn's explanation on pages 7309-7310 that a precise functional description of the

enzyme is essential for understanding how DCMTase [catalyzes the developmentally regulated patterns of DNA] methylation and for the design of novel anticancer strategies based on regulation of the enzyme is seen to be sufficient motivation to modify the internucleotide linkages and provide a pharmaceutical composition as instantly claimed." Instead, Appellants maintain that this statement by Flynn is exactly why the present application makes a substantial contribution to the art. The cited statement sets forth the need to better understand how the enzyme operates before one can develop and identify molecules that will effectively modulate the enzyme's activity without unwanted additional requirements, such as presented by antisense molecules and 5-aza-deoxycytidine. Appellants' application provides a disclosure that characterizes the enzyme and its inhibitors, with evidence that one skilled in the art of enzyme kinetics can appreciate as a solid basis for knowing that the synthetic oligonucleotide of Appellants' claims is a true inhibitor of DCMTase.

A proper determination of enzyme inhibition requires challenging the enzyme with molecules to test whether a pattern of activity change consistent with inhibition is observed. Such studies would also be designed to determine whether the regulatory effect observed is due to another molecule that may be present in the assay material.

Appellants have presented a thorough analysis with the type of data recognized in the art as demonstrating the presence of an allosteric site for modulation of DCMTase activity and ruling out active site inhibition and competitive inhibition (see Figures 12-19). Appellants have provided a thorough steady-state kinetic analysis using well-established mathematical models and three kinetic methodologies: initial velocity studies varying both substrates, dead-end inhibition and product inhibition. As discussed at page 53, lines 10-13, of the specification: "DNA substrate inhibition was common to both small, single CpG containing DNA and large, multi-site DNA. A second nucleic acid binding region on the DCMTase, distinct from the active site, is implicated from both the substrate inhibition and the dead-end inhibition studies."

At page 6 of the March 10, 2005 Office Action, the Examiner argues that "obviousness does not require absolute predictability" and implies that Flynn's teaching at pages 7309-7310 is sufficient to provide a reasonable expectation of success. "In the absence of evidence of some unexpected result or limitation that would tip the scales of patentability in applicant's favor, the claimed invention is prima facie obvious." The implication of the Examiner's argument is that every

substrate designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation is prima facie obvious as an anti-cancer agent. As discussed at page 58, lines 29-31, of Appellants' specification, "GC-box b^{MET} is distinct in form and function from previously described DCMTase inhibitors. There is a need for DCMTase inhibitors that are not incorporated into DNA and that are mechanistically unlike 5-azadeoxycytidine".

There appears to be an inference made by the Examiner at page 10 of the March 10, 2005 Office Action that the combined teachings of Flynn and Billing may have rendered the claimed GC-box b^{MET} obvious for use as an antisense molecule for inhibiting methylation thereby allegedly motivating modification of GC-box b^{MET} into GC-box p^{MET} or a pharmaceutical salt or composition. Such an inference erroneously presumes that, because Billing teaches preventing the transcription of BU101 polypeptide with a DNA oligonucleotide that is complementary to a ***unique*** region of the gene involved in transcription of that gene, one skilled in the art would have a reasonable expectation that the GC-box b^{MET} oligonucleotide could be used to somehow disrupt DCMTase methylation. Because the Examiner does not set forth an explicit technical basis for how such a disruption would occur, Applicants can only speculate as to the proposed antisense strategy.

Because one skilled in the art would not consider a GC-box a suitable antisense target for disrupting transcription in a specific manner, it is difficult to address the Examiner's inference. Assuming, however, that the Examiner is basing the rejection on an allegedly obvious use of the claimed GC-box b^{MET} oligonucleotide as an antisense molecule that would bind the GC-box involved in transcription, this allegedly obvious anti-cancer strategy is untenable. Billing suggests use of an oligonucleotide "designed to be complementary to a region of the gene involved in transcription." (See col. 26, lines 31-32.) Billing makes no suggestion or teaching to use an oligonucleotide that is complementary to transcriptional control elements common to numerous genes. Yet the inclusion of Billing as a reference supporting the obviousness rejection implies that the Examiner construes the claimed invention as oligonucleotides intended for use in an antisense strategy (which it is not).

Most genes have GC-box elements in their transcriptional control regions, but their RNA transcripts generally lack such elements. Antisense technologies aim to specifically target and interfere with the translation of proteins by hybridizing to target mRNA, or in the highly unusual

case of targeting transcription, by hybridizing to the DNA of chromosomes. Even if targeting nuclear DNA were feasible, the ubiquity of GC-box elements would result in an antisense strategy that disrupts transcription of a massive number of genes. Any inference that the claimed synthetic oligonucleotides provide an obvious antisense strategy for inhibiting DCMTase activity naively relies on an erroneous assumption that a technically reasonable level of specificity (not to mention access and efficacy) could be attained.

Appellants' claimed invention is based on a previously unknown and unexpected mechanism of inhibiting DCMTase via an allosteric site (on the enzyme, not on the DNA). The Flynn 1996 paper only describes GC-box a/b^{MET} as a substrate for the enzyme, and makes no suggestion that these substrates could serve to inhibit the enzyme. The wishful speculation in Billing (at column 26) that the diagnostic probes for breast cancer described therein could somehow be used to inhibit transcription of this breast cancer marker, and the further wish that such inhibition would actually serve as an anti-cancer treatment, cannot possibly suffice to motivate one skilled in the art to try, let alone expect success, in an anti-cancer strategy that relies upon use of Appellants' claimed synthetic oligonucleotides as antisense molecules (which they are not) disrupting transcription at GC-box elements.

Applicants urge the Examiner to consider that, to the extent the claimed oligonucleotide may appear an obvious choice as a pharmaceutical composition, this could only be through the benefit of hindsight, and without taking into account how little was known about the mechanisms of DCMTase inhibition at the time the present application was filed.

B. The Dependent Claims Are Patentable Over The Prior Art

Dependent claims 36, 37, 39, 44, 45, 47, and 48 are also submitted to be allowable over Flynn and Billing in the same manner as independent claims 31, 43, and 46, because they are dependent on independent claims 36, 37, 39, 44, 45, 47, and 48, respectively, and thus contain all the limitations of the independent claims. In addition, dependent claims 36, 37, 39, 44, 45, 47, and 48 recite a number of additional novel elements not shown by Flynn and Billing.

C. Conclusion

In light of the above arguments, Appellants respectfully submit that the cited references do not anticipate nor render obvious the claimed invention. More specifically, Appellants' claims recite novel physical features which patentably distinguish over any and all references under 35 U.S.C. §§ 102 and 103. As a result, a decision by the Board of Patent Appeals and Interferences reversing the Examiner and directing allowance of the pending claims in the subject application is respectfully solicited.

Respectfully submitted,

GATES & COOPER LLP
Attorneys for Appellants

Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045
(310) 641-8797

Date: August 10, 2005

By: _____
Name: Karen S. Canady
Reg. No.: 39,927

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G&C 30794.30-US-WO

APPENDIX

1. – 30. (Canceled)

31. (Previously Presented) A synthetic oligonucleotide of at least 26 nucleotides in length and comprising a 5mCpG dinucleotide, wherein the 5mC is a C-5 methylcytosine, and which comprises the nucleotide sequence shown in SEQ ID NO: 10, wherein the synthetic oligonucleotide comprises a phosphorothioate nucleotide.

32. – 35. (Canceled)

36. (Previously Presented) The synthetic oligonucleotide of claim 31, wherein the oligonucleotide is up to 70 nucleotides in length.

37. (Previously Presented) The synthetic oligonucleotide of claim 31, wherein the oligonucleotide is up to 50 nucleotides in length.

38. (Canceled)

39. (Previously Presented) The synthetic oligonucleotide of claim 31, wherein the oligonucleotide is 30 nucleotides in length.

40. (Canceled)

41. (Canceled)

42. (Canceled)

43. (Previously Presented) A pharmaceutically acceptable salt of a synthetic oligonucleotide of at least 26 nucleotides in length and comprising a 5mCpG dinucleotide, wherein the 5mC is a C-5 methylcytosine, and wherein the synthetic oligonucleotide comprises a phosphorothioate nucleotide.

44. (Previously Presented) A pharmaceutically acceptable salt of the synthetic oligonucleotide of claim 31.

45. (Previously Presented) A pharmaceutically acceptable salt of the synthetic oligonucleotide of claim 39.

46. (Previously Presented) A pharmaceutical composition comprising a synthetic oligonucleotide of at least 26 nucleotides in length and comprising a 5mCpG dinucleotide, wherein the 5mC is a C-5 methylcytosine, and wherein the synthetic oligonucleotide comprises a phosphorothioate nucleotide, and a pharmaceutically acceptable carrier.

47. (Previously Presented) A pharmaceutical composition comprising the synthetic oligonucleotide of claim 31 and a pharmaceutically acceptable carrier.

48. (Previously Presented) A pharmaceutical composition comprising the synthetic oligonucleotide of claim 39 and a pharmaceutically acceptable carrier.

49. – 50. (Canceled)